AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings, labeled Replacement Sheets, are attached hereto as Appendix C. Replacement Sheets include Figures 1-19. Figures 16-21 have been amended to reflect the renumbering of the figures resulting from the previous deletion of Figures 16 and 17. Original Figure 18 is now Figure 16, and so on. Figures 1-19 (as renumbered) have been formalized and the Replacement Sheets have been amended to indicate that the total number of drawing sheets is now 16. This amendment is supported by the specification and no new matter has been added.

REMARKS

Claims 1-31 are currently pending. Claims 1-19, 21, 24, 25, 28, and 29 have been withdrawn from consideration. Claims 20, 22, 23, 26, 27, 30, and 31 are rejected. Applicant has amended claims 20 and 31 for purposes of clarity. Support for the amended claims is provided in the specification. Applicant respectfully submits that the patent application and the claims, as amended, are in a condition for allowance. Accordingly, reconsideration and allowance of the claims is respectfully requested.

Specification and Drawings

Substitute Specification

Applicant respectfully submits herewith a Substitute Specification, attached hereto as Appendix A, in compliance with 37 C.F.R. §§ 1.52, 1.121(b)(3), and 1.125, to correct numerous typographical errors in the original specification and in amendments to the specification subsequently filed during the prosecution of this application. Pursuant to 37 C.F.R. § 1.125(b), the substitute specification does not include any new matter. In compliance with 37 C.F.R. § 1.125(c), a marked up copy of the substitute specification, attached hereto as Appendix B, is submitted to show all changes relative to the immediate prior version of the specification.

Applicant respectfully submits that the patent application and the claims are in a condition for allowance. Accordingly, reconsideration and allowance of the claims are respectfully requested.

Status of Disclosed U.S. Applications

The Examiner has required Applicant to "update the status of all US patent applications in the specification." Non-final Office Action, ¶ 6. Accordingly, Applicant has amended the

priority claim of the Substitute Specification to reflect the status of all U.S. applications to which the instant application claims priority. Applicant believes that this amendment addresses the Examiner's concerns and respectfully requests that the objection be withdrawn.

Amendment Filed 10/22/03 and Drawings

The Examiner has required Applicant to delete 'Figure 16. Not provided.' and 'Figure 17. Not provided.' from the specification. *See* Non-final Office Action, ¶ 7. Accordingly, Applicant has removed this text from the Substitute Specification and has corrected the text in the in the Substitute Specification to reflect the renumbering of the figures.

Additionally, in compliance with 37 C.F.R. §1.121(d), Applicant submits herewith in Appendix C Replacement Sheets 1-16 which include formal drawings and reflect the renumbering that results from the deletion of Figures 16 and 17 in the amendment filed 10/22/2003. Additionally, the Replacement Sheets indicate that the total number of drawing sheets is now 1-16.

Abstract

Examiner has objected to "[t]he abstract of the disclosure...because according to 37 CRF 1.72 (as per post AIPA changes) the abstract needs to be no more than 150 words." Non-final Office Action, ¶ 8. Accordingly, Applicant has amended the Abstract in the Substitute Specification such that the Abstract of the application is no more than 150 words. Withdrawal of the objection is respectfully requested.

MFG-hIL-2 Vector

Examiner has noted that "[t]he specification refers to the 'MG-hIL-2 vector (Figure 7)' on page 47, line 1. Figure 7 in the drawings is not a vector....The specification must be

corrected so that all references to the figures refer to the appropriate figure." Non-Final Office Action, ¶ 18. Accordingly, Applicant has amended the Substitute Specification, 45:25, to correct the typographical error of 'MG-hIL-2' to 'MFG-hIL-2' and has also corrected the figure reference to be to Figure 14. Applicant has also corrected the figure reference at 45:27 (Substitute Specification) so that the reference to the pCEP4-LTR-hIL2 vector is to Figure 15.

Nonstatutory Obviousness-type Double Patenting

The Examiner has provisionally rejected claims 20, 22, 23, 26, 27, 30, and 31 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 30-35, 46, 48, 50, and 53 of copending Application No. 10/701,359 on the grounds that the claims "are not patentably distinct from each other because whilst the two sets of claims differ in scope, both sets of claims encompass in vivo treatment of tumors with NK-92 and cytokine." Non-final Office Action, ¶ 10. Applicant will file a terminal disclaimer to overcome the double patenting rejections upon recognition of allowable subject matter.

Claim Rejections Pursuant to 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 20, 22, 23, 26, 27, 30, and 31 pursuant to 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Non-final Office Action, ¶ 12. Specifically, the Examiner alleges that "[c]laims 20, 27 are indefinite in the recitation of 'NK-92 cells' because it is unclear as to what the term encompasses." Id. In accordance with the Examiner's suggestion, Applicant has amended claim 20, on which all other claims depend, to indicate that the NK-92 cells are available at American Type Culture Collection (ATCC) as Deposit No. CRL-2407, as indicated in the Substitute Specification at

least at 16:4-5. Applicant believes that the amendment to independent claim 20 addresses Examiner's concerns and respectfully requests that the rejection be withdrawn.

Claim Rejections Pursuant to 35 U.S.C. §112, First Paragraph

The Examiner has rejected claim 31 pursuant to 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Non-final Office Action, ¶ 14.

In response, Applicant has amended claim 31 to specify "a non-solid tumor of circulating cells." The amendment is supported by the specification at least at 15:13. Applicant respectfully submits that the amendment addresses the Examiner's concerns and respectfully requests that the rejection be withdrawn.

Claim Rejections Pursuant to 35 U.S.C. § 103(a)

Gong et al. in view of Santoli et al.

Examiner has rejected claims 20, 22, 23, 26, 27, 30, and 31 pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Gong et al., *Leukemia* 8:652-658, 1994 ("Gong et al.") in view of U.S. Patent No. 5,272,082 to Santoli et al. ("Santoli et al."). Specifically, the Examiner alleges that:

> [i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Gong et al. teach use of NK-92 cells to lyse tumor cells, while Santoli et al. teach in vivo use of cytotoxic cell lines. One of ordinary skill in the art would have been motivated to do so because Santoli et al. teach

> that lytic human derived cell lines can be used in vivo to treat disease or in preclinical in vivo studies (see column 10).

Non-final Office Action, 16. For at least the reasons set forth below, Applicant respectfully traverses the rejection.

The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. In re Piasecki, 745 F.2d 1468 (Fed. Cir. 1984). To establish a *prima facie* case of obviousness, an Examiner must explicitly identify a reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1741 (2007). Prior to the issuance of the *KSR* opinion, Federal Circuit precedent taught that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the reference or combination of references must teach or disclose all of the claimed limitations of the invention. See In re Zurko, 111 F.3d 887, 42 USPQ2d 1476 (Fed. Cir. 1997). Second, and of particular importance here, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 2143.03. Third, if there is a teaching, suggestion, or incentive, it must motivate the skilled artisan to combine the teachings or suggestions with a reasonable expectation of success. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. See In re Vaeck, 947 F.2d 488; M.P.E.P. § 2143.03. Notably, while the Court in *KSR* rejected a rigid application of the teaching, suggestion, or motivation test ("the TSM test"), the Court did not reject the use of teaching, suggestion, or motivation as a factor in the obviousness analysis because most inventions rely

upon building blocks "long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." Id. In fact, the Court specifically noted that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. One court has noted that "[t]he *KSR* opinion only focused on the Federal Circuit's strict use of the TSM test in performing the obviousness analysis; it did not mention or affect the requirement that each and every claim limitation be found present in the combination of the prior art references before the analysis proceeds." Abbott Labs. V. Sandoz, Inc. 2007 U.S. Dist. Lexis 38216, *11 (N.D. Ill. 2007). Thus, *KSR* does not affect the Federal Circuit's holding that it is improper for the Examiner to use the applicant's invention as a blueprint to hunt through the prior art for the claimed elements and then combine them as claimed. See In re Zurko, 111 F.3d 887.

Gong et al. established the existence of NK-92 cells and set out to characterize the NK-92 cell line for use as a research tool, concluding that the NK-92 cell line "may provide a suitable model to study certain aspects of [Natural Killer cell/Activated-Natural Killer] cell biology." Gong et al., 658. While Gong et al. provide data that suggest that NK-92 cells kill K562 and Daudi cells in a chromium release assay (i.e., *in vitro*), there is absolutely no teaching or suggestion in Gong et al. of a method of treating a pathology *in vivo* in a mammal comprising the step of administering to the mammal a medium comprising NK-92 cells, the cells available from American Type Culture Collection (ATCC) Deposit No. CRL-2407, as in Applicant's amended claim 20. As such, one skilled in the art would not be motivated to look to Santoli et al. for such methods of *in vivo* treatment.

Additionally, Santoli et al. teach "genetically modified cytotoxic T lymphoblastic leukemia cell lines (T-ALL), and uses of these cell lines in cancer therapy." Santoli et al., Abstract. Santoli et al. do not disclose NK-92 cells or methods of the present invention. Rather, they disclose the T-ALL cell lines 104, 107 and 103/2 and their use to treat cancer, both *in vivo* and *ex vivo* (10:30-60). NK-92 cells are not disclosed, nor is their use described. Applicant notes that the T-ALL cells are vastly different from the NK-92 cells claimed by Applicant. For example, their membrane protein profile suggests that T-ALL cells are of T-cell origin, while NK-92 cells, lacking the typical CD3 marker protein, are derived specifically from natural killer cells, lacking the T-cell receptor complex (TCR). Furthermore, the use of T-ALL cells is complicated: sub-culturing requires passage through mice. Finally, NK-92 cells have unusual requirements for sub-culturing. When cultured in α-minimum essential medium (α-MEM), the American Type Culture Collection (ATCC; Manassas, VA) recommends the media be supplemented with, among other things, 0.2 mM inositol, 0.1 mM 2-mercaptoethanol, 0.02 mM folic acid, 100-200 U/ml recombinant IL-2 (otherwise the cells die after 72 hours), and most surprisingly, a large proportion (25%) of two sera: 12.5% horse serum and 12.5% fetal bovine serum (FBS). In earlier passages, hydrocortisone is necessary. The cell density in culture is critical, and must be regularly checked and regulated by medium changes. The medium formulation, IL-2 concentration, serum concentration and cell density must be carefully regulated throughout the culture period. The culture of these cells are in stark contrast to other well-established cell lines (or even hybridomas), such as Madin-Darby Canine Kidney (MDCK) cells, which can thrive in simple MEM with 5% (FBS) and 2mM L-glutamine, 10mM N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), and sub-culturing once or twice a

week. The T-ALL cells taught by Santoli et al. are functionally and structurally distinct from the NK-92 cells of Applicant's claimed invention. In fact, Santoli et al. actually teach away from the use of NK-92 cells, stating that the T-ALL cells meet the "need in the art for therapeutic methods and compositions thereof for cancers which can utilize cytotoxic T cell lines and avoid the present need in conventional LAK therapy for patient's own killer cells, and which can target selected organs (e.g., brain, liver, lung) which are sites of metastases." Santoli et al., 2:33-38. For at least these reasons, Gong et al., alone or in combination with Santoli et al., fails to teach or suggest a method of treating a pathology *in vivo* in a mammal comprising the step of administering to the mammal a medium comprising NK-92 cells (ATCC Deposit No. CRL-2407), as is claimed in Applicant's amended claim 20. Therefore, Applicant respectfully submits that neither independent claim 20 nor claims 22, 23, 26, 27, 30, or 31 depending therefrom are obviated by Gong et al. alone or in combination with any cited reference because the reference, alone or in combination, fails to teach or suggest all of the claim limitations. *See* M.P.E.P. § 2143.03. Applicant respectfully requests that the rejection be withdrawn.

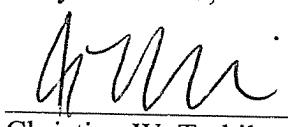
Conclusion

Applicant respectfully submits that the patent application and the claims are in a condition for allowance. Accordingly, reconsideration and allowance of the claims are respectfully requested.

Applicant would appreciate the courtesy of a telephone call should the Examiner have any questions or comments with respect to this response or the claim language for purposes of efficiently resolving same.

The Commissioner is hereby authorized to charge Deposit Account No. 03-2026 for any fees associated with this Request for Continued Examination.

Respectfully submitted,

By 

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